MAYO CLINIC LABORATORIES

# Test Definition: MFRGG

Marfan, Loeys-Dietz, and Aortopathy Gene Panel, Varies

## Overview

### Useful For

Providing a genetic evaluation for patients with a personal or family history suggestive of Marfan syndrome and related conditions

Establishing a diagnosis for Marfan syndrome, Loeys-Dietz syndrome, vascular Ehlers-Danlos syndrome, classic Ehlers-Danlos syndrome, and heritable thoracic aortic disease/aortopathy

### Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide and copy number variants in 30 genes associated with Marfan syndrome, Loeys-Dietz syndrome, vascular Ehlers-Danlos syndrome, hereditary aortopathies, and related phenotypes: *ACTA2, ADAMTS10, ADAMTS17, BGN, CBS, COL3A1, COL5A1, COL5A2, EFEMP2, FBN1, FBN2, FLNA, LOX, LTBP3, MED12, MFAP5, MYH11, MYLK, NOTCH1, PRKG1, SKI, SLC2A10, SMAD2, SMAD3, SMAD4, SMAD6, TGFB2, TGFB3, TGFBR1,* and *TGFBR2*. See Targeted Genes and Methodology Details for Marfan, Loeys-Dietz, and Aortopathy Gene Panel and Method Description for additional details.

Identification of a pathogenic variant may assist with diagnosis, prognosis, clinical management, familial screening, and genetic counseling for Marfan syndrome, Loeys-Dietz syndrome, vascular Ehlers-Danlos syndrome, hereditary aortopathies, and related phenotypes.

Prior Authorization is available for this assay.

### Special Instructions

- Informed Consent for Genetic Testing
- Informed Consent for Genetic Testing (Spanish)
- Connective Tissue/Cerebrovascular Disease Genetic Testing Patient Information
- Targeted Genes and Methodology Details for Marfan, Loeys-Dietz, and Aortopathy Gene Panel
- Marfan and Related Conditions Panel (MFRGG) Prior Authorization Ordering Instructions

### Method Name

Sequence Capture and Targeted Next-Generation Sequencing followed by Polymerase Chain Reaction (PCR) and Sanger Sequencing

### NY State Available

Yes

## Specimen

### Specimen Type

Varies

## Ordering Guidance

Upon request and after initial testing is complete, WESPR / Panel to Whole Exome Sequencing Reflex Test, Varies may be added to this test. To obtain more information about this option or add WESPR testing, call 800-533-1710.

Customization of this panel and single gene analysis for any gene present on this panel are available. For more information see CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies.

Targeted testing for familial variants (also called site-specific or known mutations testing) is available for the genes on this panel. See FMTT / Familial Variant, Targeted Testing, Varies. To obtain more information about this testing option, call 800-533-1710.

## Shipping Instructions

Specimen preferred to arrive within 96 hours of collection.

## Necessary Information

Prior Authorization is available, **but not required**, for this test. If proceeding with the prior authorization process, submit the required form with the specimen.

## Specimen Required

**Patient Preparation:** A previous bone marrow transplant from an allogenic donor will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.
**Specimen Type:** Whole blood
**Container/Tube:**
**Preferred:** Lavender top (EDTA) or yellow top (ACD)
**Acceptable:** Any anticoagulant
**Specimen Volume:** 3 mL
**Collection Instructions:**
1. Invert several times to mix blood.
2. Send whole blood specimen in original tube. **Do not aliquot.**
**Specimen Stability Information:** Ambient (preferred)/Refrigerated

## Forms

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available:
-Informed Consent for Genetic Testing (T576)
-Informed Consent for Genetic Testing (Spanish) (T826)
2. Connective Tissue/Cerebrovascular Disease Genetic Testing Patient Information
3. Marfan and Related Conditions Panel (MFRGG) Prior Authorization Ordering Instructions
4. If not ordering electronically, complete, print, and send a Cardiovascular Test Request Form (T724) with the specimen.

## Specimen Minimum Volume

1 mL

### Reject Due To

All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

### Specimen Stability Information

| Specimen Type | Temperature | Time | Special Container |
|---|---|---|---|
| Varies | Varies | | |

## Clinical & Interpretive

### Clinical Information

Marfan syndrome (MFS) is an autosomal dominant genetic disorder affecting the connective tissue that occurs in approximately 1 to 2 per 10,000 individuals. It is characterized by the presence of skeletal, ocular, and cardiovascular manifestations and is caused by variants in the *FBN1* gene. Skeletal findings may include tall stature, chest wall deformity, scoliosis, and joint hypermobility. Lens dislocation (ectopia lentis) is the cardinal ocular feature, with mitral valve prolapse and aortic root dilatation/dissection the main cardiovascular features.(1)

Loeys-Dietz syndrome (LDS) is an autosomal dominant connective tissue disease with significant overlap with Marfan syndrome but may include involvement of other organ systems and is primarily caused by variants in the *TGFBR1* and *TGFBR2* genes.(2,3) Features of LDS that are not typical of MFS include craniofacial and neurodevelopmental abnormalities and arterial tortuosity with increased risk for aneurysm and dissection throughout the arterial tree. Variants in the *SMAD3* gene have been reported in families with an LDS-like phenotype with arterial aneurysms and tortuosity and early onset osteoarthritis. Variants in the *TGFB3* gene have also been reported in families with an LDS-like phenotype, although these individuals tend to not have arterial tortuosity.

Heritable thoracic aortic disease, also known as familial thoracic aortic aneurysm/dissection (FTAAD), is a genetic condition primarily involving dilatation and dissection of the thoracic aorta but may also include aneurysm and dissection of other arteries. This condition has a highly variable age of onset and presentation and may involve additional features such as congenital heart defects and other features of connective tissue disease or smooth muscle abnormalities depending on the causative gene. The gene most commonly involved in FTAAD is *ACTA2*.(4,5)

Vascular Ehlers-Danlos syndrome (also known as vEDS or EDS IV) is an autosomal dominant connective tissue disease caused by variants in the *COL3A1* gene. vEDS may present with characteristic facial features, thin, translucent skin, easy bruising, and arterial, intestinal, and uterine fragility. Arterial rupture may be preceded by aneurysm or dissection or may occur spontaneously.(6) Classic Ehlers-Danlos syndrome types I and II (also known as cEDS) are caused by variants in the *COL5A1* and *COL5A2* genes. Aortic root dilation and, more rarely, spontaneous vessel rupture have been reported in cEDS.(7)

Other genes included on this panel are associated with less common conditions that have significant overlap with Marfan syndrome, Loeys-Dietz syndrome, vEDS, and cEDS.

### Reference Values

An interpretive report will be provided.

## Interpretation

All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(8) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

## Cautions

Clinical Correlations:
Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

If testing was performed because of a clinically significant family history, it is often useful to first test an affected family member. Detection of a reportable variant in an affected family member would allow for more informative testing of at-risk individuals.

To discuss the availability of additional testing options or for assistance in the interpretation of these results, contact the Mayo Clinic Laboratories genetic counselors at 800-533-1710.

Technical Limitations:
Next-generation sequencing may not detect all types of genomic variants. In rare cases, false-negative or false-positive results may occur. The depth of coverage may be variable for some target regions; assay performance below the minimum acceptable criteria or for failed regions will be noted. Given these limitations, negative results do not rule out the diagnosis of a genetic disorder. If a specific clinical disorder is suspected, evaluation by alternative methods can be considered.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. Confirmation of select reportable variants will be performed by alternate methodologies based on internal laboratory criteria.

This test is validated to detect 95% of deletions up to 75 base pairs (bp) and insertions up to 47 bp. Deletions-insertions (delins) of 40 or more bp, including mobile element insertions, may be less reliably detected than smaller delins.

Deletion/Duplication Analysis:
This analysis targets single and multi-exon deletions/duplications; however, in some instances single exon resolution cannot be achieved due to isolated reduction in sequence coverage or inherent genomic complexity. Balanced structural rearrangements (such as translocations and inversions) may not be detected.

Deletion/duplication events that extend past the genes included on the panel may occur. In these instances, genes included in the ordered test are provided on the report and interpreted, and genomic breakpoints are reported if they are confirmed. However, copy number variants for genes not listed in the Method Description are typically not reported or interpreted for haploinsufficiency/triplosensitivity. CMACB / Chromosomal Microarray, Congenital, Blood; WESPR / Panel to Whole Exome Sequencing Reflex Test, Varies; or WGSDX / Whole Genome Sequencing for Hereditary Disorders, Varies is recommended for a full interpretation of deletions/duplications predicted to extend past the genes included on

the panel.

This test is not designed to detect low levels of mosaicism or to differentiate between somatic and germline variants. If there is a possibility that any detected variant is somatic, additional testing may be necessary to clarify the significance of results.

Genes may be added or removed based on updated clinical relevance. Refer to the Targeted Genes and Methodology Details for Marfan, Loeys-Dietz, and Aortopathy Gene Panel for the most up to date list of genes included in this test. For detailed information regarding gene specific performance and technical limitations, see Method Description or contact a laboratory genetic counselor.

If the patient has had an allogeneic hematopoietic stem cell transplant or a recent blood transfusion, results may be inaccurate due to the presence of donor DNA. Call Mayo Clinic Laboratories for instructions for testing patients who have received a bone marrow transplant.

Reclassification of Variants:
At this time, it is not standard practice for the laboratory to systematically review previously classified variants on a regular basis. The laboratory encourages healthcare providers to contact the laboratory at any time to learn how the classification of a particular variant may have changed over time.

Variant Evaluation:
Evaluation and categorization of variants are performed using published American College of Medical Genetics and Genomics and the Association for Molecular Pathology recommendations as a guideline.(8) Other gene-specific guidelines may also be considered. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Variants classified as benign or likely benign are not reported.

Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and periodic updates to these tools may cause predictions to change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Rarely, incidental or secondary findings may implicate another predisposition or presence of active disease. Incidental findings may include, but are not limited to, results related to the sex chromosomes. These findings will be carefully reviewed to determine whether they will be reported.

## Clinical Reference

1. Loeys BL, Dietz HC, Braverman AC, et al: The revised Ghent nosology for the Marfan syndrome. J Med Genet. 2010 Jul;47(7):476-485
2. Loeys BL, Schwarze U, Holm T, et al: Aneurysm syndromes caused by mutations in the TGF-beta receptor. N Engl J Med. 2006 Aug 24;355(8):788-798
3. Loeys BL, Chen J, Neptune ER, et al: A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2. Nat Genet. 2005 Mar;37(3):275-281
4. Milewicz DM, Regalado E: Heritable thoracic aortic disease overview. In: Adam MP, Ardinger HH, Pagon RA, et al, eds.

GeneReviews [Internet]. University of Washington, Seattle; 2003. Updated December 14, 2017. Accessed September 22, 2021. Available at www.ncbi.nlm.nih.gov/books/NBK1120/
5. Guo DC, Pannu H, Tran-Fadulu V, et al: Mutations in smooth muscle a-actin (ACTA2) lead to thoracic aortic aneurysms and dissections. Nat Genet. 2007 Dec;39(12):1488-1493
6. Pepin M, Schwarze U, Superti-Furga A, Byers PH: Clinical and genetic features of Ehlers-Danlos syndrome type IV, The vascular type. N Engl J Med. 2000 Mar 9;342(10):673-680
7. Malfait F, Wenstrup R, Paepe AD: Classic Ehlers-Danlos syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2007. Updated July 26, 2018. Accessed August 1, 2022. Available at www.ncbi.nlm.nih.gov/books/NBK1244/
8. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424

## Performance

### Method Description

Next-generation sequencing (NGS) and/or Sanger sequencing are performed to test for the presence of variants in coding regions and intron/exon boundaries of the genes analyzed, as well as some other regions that have known disease-causing variants. The human genome reference GRCh37/hg19 build was used for sequence read alignment. At least 99% of the bases are covered at a read depth over 30X. Sensitivity is estimated at above 99% for single nucleotide variants, above 94% for deletions-insertions (delins) less than 40 base pairs (bp), above 95% for deletions up to 75 bp and insertions up to 47 bp. NGS and/or a polymerase chain reaction-based quantitative method is performed to test for the presence of deletions and duplications in the genes analyzed.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. See Targeted Genes and Methodology Details for Marfan, Loeys-Dietz, and Aortopathy Gene Panel for details regarding the targeted genes analyzed for each test and specific gene regions not routinely covered.(Unpublished Mayo method)

Confirmation of select reportable variants may be performed by alternate methodologies based on internal laboratory criteria.

Genes analyzed: *ACTA2, ADAMTS10, ADAMTS17, BGN, CBS, COL3A1, COL5A1, COL5A2, EFEMP2, FBN1, FBN2, FLNA, LOX, LTBP3, MED12, MFAP5, MYH11, MYLK, NOTCH1, PRKG1, SKI, SLC2A10, SMAD2, SMAD3, SMAD4, SMAD6, TGFB2, TGFB3, TGFBR1,* and *TGFBR2*

### PDF Report

No

### Day(s) Performed

Varies

### Report Available
28 to 42 days

### Specimen Retention Time
Whole blood: 2 weeks (if available); Extracted DNA: 3 months

### Performing Laboratory Location
Mayo Clinic Laboratories - Rochester Main Campus

## Fees & Codes

### Fees
- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact Customer Service.

### Test Classification
This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. It has not been cleared or approved by the US Food and Drug Administration.

### CPT Code Information
81410

### Prior Auhtorization
Insurance preauthorization is available for this testing; forms are available.

Patient financial assistance may be available to those who qualify. Patients who receive a bill from Mayo Clinic Laboratories will receive information on eligibility and how to apply.

### LOINC® Information

| Test ID | Test Order Name | Order LOINC® Value |
|---|---|---|
| MFRGG | Marfan and Related Conditions Panel | 105198-6 |

| Result ID | Test Result Name | Result LOINC® Value |
|---|---|---|
| 617380 | Test Description | 62364-5 |
| 617381 | Specimen | 31208-2 |
| 617382 | Source | 31208-2 |
| 617383 | Result Summary | 50397-9 |
| 617384 | Result | 82939-0 |
| 617385 | Interpretation | 69047-9 |
| 617386 | Additional Results | 82939-0 |

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|---|---|---|
| 617387 | Resources | 99622-3 |
| 617388 | Additional Information | 48767-8 |
| 617389 | Method | 85069-3 |
| 617390 | Genes Analyzed | 48018-6 |
| 617391 | Disclaimer | 62364-5 |
| 617392 | Released By | 18771-6 |